International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.3, No.3,pp 1369-1374, July-Sept 2011

Application of Optimization techniques in the Microwave-assisted Organic synthesis of some Schiff's bases

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Abstract: Optimization techniques are widely applicable as analytical tools in pharmaceutical field. These consist of experimental design, mathematical model and graphical outcomes which yields optimum results. The objective of this study was to develop an optimized formula for microwave assisted synthesis of Schiff's bases by using suitable optimization techniques. A 2^3 factorial design was employed for the microwave assisted synthesis with microwave power, molar ratio and time as independent variables and yield as dependent variable. Reaction of 2-(2-methyl-1H-benzimidazol-1-yl)-acetohydrazide (**1**) with appropriate aromatic aldehydes yielded corresponding Schiff's bases (**2a-2h**). These reactions were carried out under microwave irradiations, hence can be termed as green synthesis reactions.
Key words: Schiff's bases, Optimization, 2^3 Factorial design.

INTRODUCTION

Design and development of an immaculate drug product, drug intermediate or pharmaceutical process involves multiple objectives. Since long time this task has been fulfilled through trial and error method, which has several disadvantages like utilization of more time, energy and resources. These issues can be sorted out by the use of optimization techniques. Optimization techniques need lesser experimentations to achieve optimum results. Optimization techniques comprises of experimental design, mathematical models and graphical outcomes [1]. The application of factorial design in pharmaceutical formulation development has played a key role in understanding the relationship between the independent variables and response to them. The independent variables are controllable whereas responses are dependent variables.

Heterocyclic compounds constitute about sixty-five percent of organic chemistry literature and are widely distributed in nature [2]. Among nitrogen containing fused heterocycles, 2-methyl benzimidazole has a large aromatic group substituted to the imidazole ring causing hydrophobic hydration effect. On the other hand, the existence of the two hydrophilic nitrogen groups in the inidazole molecule could imply specific interactions between them, as well as with bulk solvent structure, strongly changing the solubility of the solutes under investigation. The cytotoxicity of 2-methyl benzimidazole derivatives was investigated against a variety of cell lines where, introduction of various heterocylic rings at the position 5 of 2-methyl benzimidazole led to discovery of potent antitumor derivatives. [3, 4]

Schiff's bases of various heterocyclic scaffolds exhibit variety of biological activities like anti-HIV [5, 6], anti-cancer [7], antibacterial [8], fungicidal [9] and anti-inflammatory [10] and anti ulcer [11].

In view of this, in present work various 2-methyl benzimidazole based Schiff's bases were synthesized under microwave radiations and the reaction parameters were so optimized that maximum yield can be achieved.

MATERIALS AND METHODS

All the chemicals viz. 2-methyl benzimidazole, hydrazine hydrate, various aromatic aldehydes were purchased from S.D. Fine Chem. India Ltd. Mumbai. Solvents were used only after distillation for the synthesis. Microwave assisted synthesis was carried out using Catalyst Microwave type oven, Pune, ranging from power levels 1-9 at 140-700 watt. Optimization software was run using Design expert software, *Statease 7.1.6* available trial version free of cost online.

In this work, 2-(2-methyl-1H-benzimidazol-1-yl)-acetohydrazide (1) [12] was reacted with appropriate aromatic aldehydes in presence of catalytic amount of glacial acetic acid to afford the Schiff's bases (2a-2h). The detail of microwave assisted synthesis of titled compounds is presented elsewhere [12].

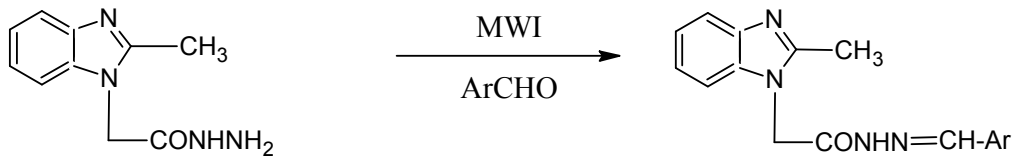
OPTIMIZATION

For optimization of a chemical reaction, it is important to consider the various factors that governs the over all reaction. Here in microwave power, molar ratio of reactants and time were considered as the three significant independent factors. The response would be dependent factor i.e. percentage yield. The 3 independent factors were considered at 2 levels i.e. high and low levels. Thus 2^3 factorial design was employed to optimize the reactions**.**

Optimization of Microwave Assisted Synthesis of compound 2a:

The parameters considered in the optimization of microwave assisted synthesis of **2a** were molar ratio of reactants (i.e.hydrazide **(1)** and benzaldehyde), time required to complete the reaction in minutes and microwave power in watts. **Table No.1** denotes the different levels of the experimental procedure and the factors used. The various combinations of factors and levels were used after appropriate permutation and grouping was done.

SCHEME



1 **2a-2h**

Fig. 1: Scheme of synthesis.

Table No. 1: Different Levels and Factors Used In Experimental Model:

FACTORS	LEVELS	
	HIGH	**LOW**
MOLAR RATIO (A)	1.5	1.2
POWER(B)	560	455
TIME(C)	60	40

Based on the responses and the factors **Table no.2** was constructed using the free trial software *Statease 7.1.6.*

Table No. 2: Optimization Design for compound 2a.

Std	Run	Factor A: No. of moles	Factor B: Power (Watts)	Factor C:Time (minutes)	Response % Yield
2	1	2.5	490	40	68
6	2	2.5	490	60	78
1	3	2.2	490	40	64
3	4	2.2	560	40	83
7	5	2.2	560	60	84
4	6	2.5	560	40	89
5	7	2.2	490	60	71
8	8	2.5	560	60	95

Based on the summary sheet, yield analysis was performed. In yield analysis, the Quadratic model was found to be significant. Thus the ANOVA was generated as demonstrated in **Table No. 3.** This was followed by determination of Standard error and coefficient as mentioned in **Table No. 4.** This generated a regression **Equation 1** as given below;

Equation 1: % Yield = -122.083 + 23.3333xA + 0.25xB + 0.3xC

Table No. 3: Analysis of variance (ANOVA) table for yield analysis of compound **2a.**

Source	Sum of Squares	DF	Mean Square	F Value	p-value Prob > F	Remark
Model	782.5	3	260.8333	40.91503	0.0018	significant
A-No. of moles	98	1	98	15.37255	0.0172	
B-Power	612.5	1	612.5	96.07843	0.0006	
C-Time	72	1	72	11.29412	0.0283	
Residual	25.5	4	6.375			
Cor Total	808	7				

DF: Degree of freedom; **Cor total**: Corrected total; **F-Value:** Fixation Indice or Fisher - Snedecor distribution.

Table No. 4: Details of Coefficient and Standard Error for yield analysis of compound 2a.

Factor	Coefficient Estimate	DF	Standard Error	95% CI Low	95% CI High	VIF
Intercept	79	1	0.892679	76.52153	81.47847	
A-No. of moles	3.5	1	0.892679	1.021527	5.978473	1
B-Power	8.75	1	0.892679	6.271527	11.22847	1
C-Time	3	1	0.892679	0.521527	5.978473	1

DF: Degree of freedom; **CI:** Confidence Interval; **VIF**: Variance Inflation Factor.

Once the model was found to be significant, the graphical plots were generated. The 3-D surface response and contour plot were plotted. The **Fig.1** gives a three dimensional view of the effect of each independent parameter (i.e. number of moles, time and microwave power) on dependent parameters (i.e percentage yield). The overview denotes regions in the graph where the percentage yield of compound **2a** ranges from 64 % - 95 %. A similar data is projected through a 2-D Contour Plot as shown in **Fig.2.**

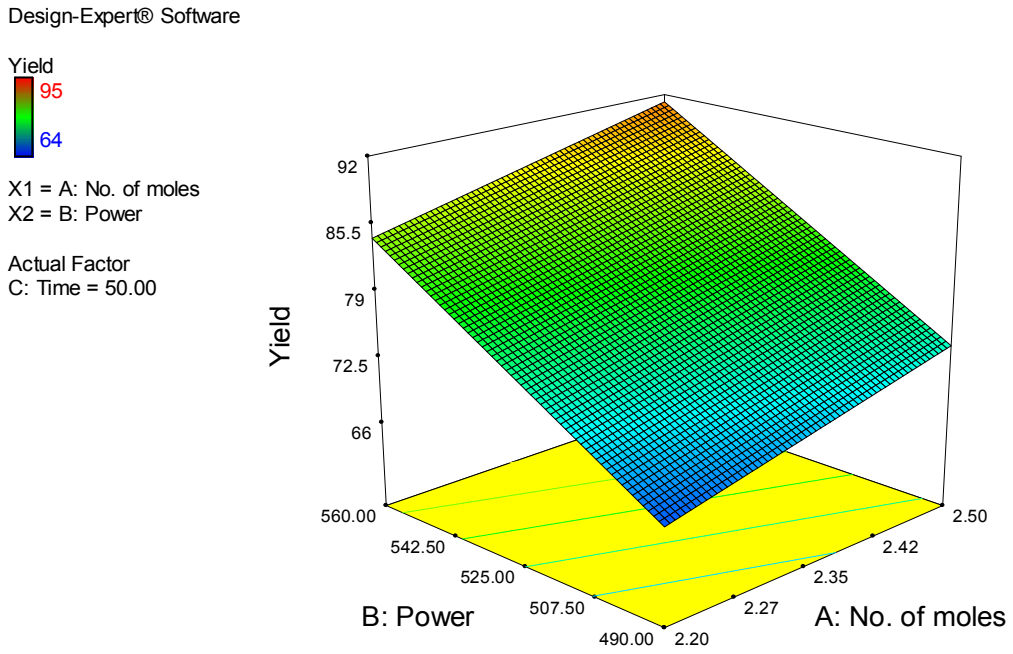


Fig. 1: 3-D Surface Response curve for yield analysis of Compound 2a

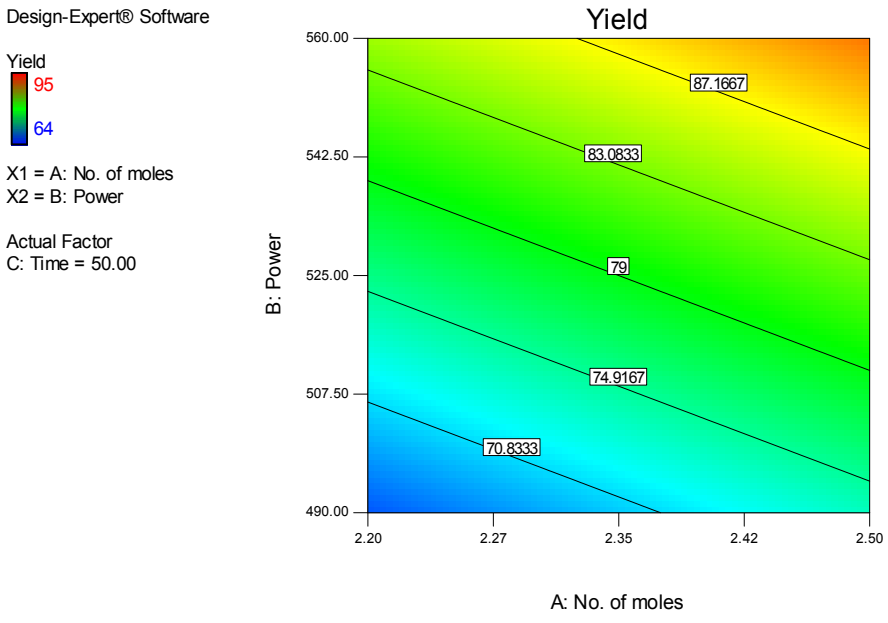


Fig. 2: 2-D Contour plot for yield analysis of Compound 2a

Similarly such analysis was performed for rest of all the compounds **(2b- 2d**).

RESULTS AND DISCUSSION

The optimized solutions for **2a** (**Table No.5**) were compared and it was found that Solution 1 gave the highest possible yield. But the time required for completion of the reaction was more than that of the other solutions and the power required was more as compared to others. Looking through all the 20 solutions, solution 1-10 could be the best possible optimized results and others were near about the best possible optimized condition for the synthesis of the Schiff's base (**2a**).Thus, molar proportion of 1:1.5 at 560 watts within the time of 60 minutes gave maximum yield i.e. 94.25 % whilst other solutions reported the yield value in the range of 90.49 - 94.20 %.

Optimized solutions suggested by the software for synthesis of **2b** were, molar proportion of 1:1.5 at 560 watts within time of 60 minutes yielding 91.74% of the compound. For **2c**, yield ranging from 74.74 - 86.96 % using molar proportion of 1:1.5 and microwave power of 560 watts in 60 minutes were the best possible optimized conditions.

Finally for **2d,** the molar proportion of 1:1.5 at 560 watts within time of 60 minutes resulted into maximum yield of 85 %.

CONCLUSION

Conventional method of synthesis is slow and non-uniform. On the other hand microwave irradiation produces efficient internal heating by direct coupling of microwave energy with polar molecules. Optimizing the various variables helped achieve an economical and eco-friendly methodology for the synthesis of Schiff's bases. The optimum solutions for percentage yield depended on the factors like molar ratio, power and time. Experiments performed showed that maximum yield was obtained when experiment was carried out using molar proportion of 1:1.5 between hydrazide and aldehydes respectively, at power of 560 watts within the time of 60 minutes**.** The results were more refined in the case of software. Thus it can be concluded that the optimum solutions are super-imposable and pose to be the best conditions to synthesize the series of Schiff's bases under microwave.

Table No. 5: Solution for optimum conditions required for microwave assisted synthesis of compound 2a:

Solution	No. of moles	Power (Watts)	Time (Minutes)	% Yield	Desirability
1	2.5	560	60	94.25	1
2	2.497995	559.9996	59.99996	94.2031	1
3	2.499644	560	59.74313	94.16462	1
4	2.495474	559.9999	59.99995	94.14437	1
5	2.49942	559.1691	59.99992	94.02871	1
6	2.5	560	59.32382	94.04713	1
7	2.499999	558.113	59.99999	93.77824	1
8	2.5	559.9998	59.15893	93.99762	1
9	2.5	556.7613	59.99994	93.44031	1
10	2.499999	560	58.26686	93.73003	1
11	2.5	559.9997	57.80718	93.59208	1
12	2.5	554.0216	60	92.75538	1
13	2.5	560	57.57293	93.52187	1
14	2.499999	552.45	59.99996	92.36248	1
15	2.5	550.4829	59.99986	91.87068	1
16	2.5	548.7926	59.99988	91.44811	1
17	2.5	559.9996	55.76707	92.98001	1
18	2.5	560	55.56527	92.91957	1
19	2.499999	559.9999	54.94115	92.7323	1
20	2.5	544.974	59.99997	90.4935	1

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